lution of both measurable and evaluable disease needs to be taken into account for future response definition.[4] This also holds partly true for nonevaluable MPM disease (like pleural effusion or ascites) because, for objective complete tumor response, nonevaluable MPM disease needs to be completely absent. In MPM patients with nonevaluable disease only where no complete response is present, no other MPM disease status can be assessed.

As a suggestion, therefore, and in expectation of possible newer evaluation tools for MPM,[2] we would like to propose the authors to provide clinicians with a complete practical guide on how to make radiologic measurements and evaluations of all possible MPM cases, presenting mostly with measurable, sometimes non-measurable, and occasionally with evaluable-only pleural disease.

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Reply to the Letter to the Editor Entitled A Practical Guide to Measure "All" Malignant Pleural Mesothelioma Tumors by Modified RECIST Criteria?

In Reply:

We fully agree with Nackaerts et al. that there are significant radiographic challenges encountered when measuring thoracic mesothelioma tumors. As pointed out, mesothelioma is not always measurable by computed tomography (CT), magnetic resonance imaging, or positron emission tomography (PET) scans, and the classification of "nonmeasurable but evaluable" is a common conundrum. However, given our limitations with cost, technology availability, and consistency in radiographic measurements, the standard of care in cooperative group trials is to measure thoracic mesothelioma tumors with serial CT scans. Modified RECIST criteria by Byrne and Nowak[1] is the preferred method of evaluating pleural tumors on CT scans as pleural disease measurements, using the short-axis rather than the long-axis diameter, appear to correlate better with clinical outcome. Given the rare incidence of mesothelioma and occasional confusion on how to measure pleural rinds, the intent of our recent publication[2] was to serve as a practical guide (a step-by-step manual) to enhance consistency in disease measure-ments for the Southwest Oncology Group institutions.

We concur with Nackaerts et al. that our current measurement practice is not optimal, and future studies of technology are vital to develop better and more consistent measurements. In our recent publication, we did not intend to write a review on the different imaging modalities of measuring mesothelioma, which was clearly summarized in the recent publication by Nowak et al.[3] The dilemma of measuring the "nonmeasurable but evaluable" mesothelioma tumors is that there is currently no technology that has been validated or consistently accurate. The labor-intensive strategy of area measurements rather than linear measurements would be impractical for a cooperative group to undertake, as not all investigators would have the resources, time, or expertise to conduct this study. While fluorodeoxyglucose PET and PET-CT scans are gaining popularity in imaging mesothelioma, and does show some promise, there are multiple factors that cause standardized uptake value measurements to vary from the initial baseline study to subsequent serial studies; and there is neither consensus nor validation of response criteria for mesothelioma. Some studies[4–6] have previously reported a correlation to clinical outcome using either a metabolic response by measuring maximum standardized uptake values or total glycolytic volume; however, these trials are small in number and other studies[7,8] have reported conflicting results. It is clear that additional prospective trials with radiographic correlates are needed to validate and develop new strategies based on our current technical capabilities; we hope that future research, perhaps new novel PET tracers, will overcome the complexity of measuring this nonspherical tumor.

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How Should We Use Bevacizumab in Patients with Non-small Cell Lung Cancer?

To the Editor:

The first phase III study of bevacizumab in combination with chemotherapy in patients with nonsquamous non-small cell lung cancer (E4599) was conducted in the United States, and both progression-free survival (PFS) and overall survival (OS) were significantly improved in the bevacizumab arm[1]: however, in the second phase III study (AVAiL) conducted in the European Union, there was no significant difference in OS.[2]

When clinicians make a treatment decision, there are three important points to be considered: whether it prolongs OS, whether it improves patients' quality of life, and how much it costs. Regarding bevacizumab, the cost is high, and its toxicity could compromise quality of life and sometimes lead to serious conditions, such as pulmonary hemorrhage and thromboembolism. Therefore, OS improvement is necessary by using bevacizumab; however, only one phase III study has shown a survival advantage of bevacizumab as mentioned above. Consequently, skeptical oncologists do not use bevacizumab for non-small cell lung cancer patients even if they are free from contraindications.

Table 1 summarizes the results of three randomized studies of bevacizumab, E4599,[1] AVAiL,[2] and a Japanese phase II study (JO19907).[3] As shown from the improved response rate and PFS, bevacizumab has reproducibly demonstrated a strong antitumor effect throughout the studies; however, only the E4599 study demonstrated improved OS. How could we use this potent drug appropriately?

TABLE 1. Randomized Studies of First-Line Bevacizumab in Combination with Chemotherapy in NSCLC

	E4599			AVAiL				JO19907		
Bev	—	15 mg		—	7.5 mg	15 mg		—	15 mg	
N	444	434		347	345	351		59	121	
RR (%)	15	35		20	34	30		31	61	
PFS (mo)	4.5	6.2	HR 0.66	6.1	6.7	6.5	HR 0.75 (7.5 mg) 0.82 (15 mg)	5.9	6.3	HR 0.61
OS (mo)	10.3	12.3	HR 0.79	13.7	14.1	14.5	HR 0.94 (7.5 mg) 0.97 (15 mg)	23.4	22.8	HR 0.99

NSCLC, non-small cell lung cancer; RR, response rate; PFS, progression-free survival; OS, overall survival; HR, hazard ratio.

Broglio and Berry[4] addressed the importance of survival postprogression (SPP) and pointed out that lack of statistical significance in OS does not necessarily imply lack of improvement in OS, especially when SPP is longer than 12 months. Despite the recent development of efficient second- or third-line chemotherapy, SPP longer than 12 months is not so common, except in patients with activating epidermal growth factor receptor (EGFR) mutations. It seems quite reasonable to assume that more than 30% of included patients (East-Asian, nonsquamous) had EGFR mutations and would have received EGFR-tyrosine kinase inhibitor when disease progressed in each arm, and the marked improvement of OS in those patients might have negated the significant difference in PFS in the JO19907 study.

Collectively, bevacizumab in combination with chemotherapy may be more recommendable for patients with wild-type EGFR than patients with EGFR mutations in the current situation. As for patients with EGFR mutants, the recently published BeTa study,[5] a randomized phase III study comparing second-line erlotinib with or without bevacizumab, may be useful. In this study, PFS doubled (3.4 versus 1.7 months, hazard ratio [HR]: 0.62), but OS was almost identical (9.3 versus 9.2 months, HR: 0.97). Interestingly, the improvement of OS was more prominent in EGFR mutants (HR: 0.44) than EGFR wild-type (HR: 1.11) in subgroup analysis. As the authors mentioned,

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